Message

From: Subramaniam, Ravi [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=E738F9D27062486E9047184B867FD968-SUBRAMANIAM, RAVI]
Sent: 4/29/2014 5:28:26 PM
To: Kraft, Andrew [Kraft.Andrew@epa.gov]
Subject: RE: Paul

I am just giving up, going home, and burying my head somewhere.

Ravi.

Ravi Subramaniam, PhD; Associate, Quantitative Methods Branch, IRIS Division, NCEA-ORD, US EPA
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From: Kraft, Andrew
Sent: Tuesday, April 29, 2014 1:26 PM
To: Subramaniam, Ravi; Glenn, Barbara
Subject: RE: Paul

Wow. I guess now would be a good time for you to refer him to the Agenda.

From: Subramaniam, Ravi
Sent: Tuesday, April 29, 2014 1:24 PM
To: Kraft, Andrew; Glenn, Barbara
Subject: Paul

Would you believe it? Paul says he does not know anything about the questions we are posing!

Ravi.

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From: Schlosser, Paul
Sent: Tuesday, April 29, 2014 12:38 PM
To: Subramaniam, Ravi
Subject: RE: "slides" (Endogenous formaldehyde workshop)

You said that on the phone yesterday. I'm not sure I have those questions. The following is what's on the 'home' page for the meeting:

- Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde and implications for the health assessment;
- Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and
- Epidemiological research examining the potential association between formaldehyde exposure and these cancers.

What I was doing did not demonstrate evidence pertaining to the influence of endogenous formaldehyde on the toxicity of exogenous, although I assumed that dG levels were in some way a measure of risk. And it didn't address points 2 or 3 either.

If there were other questions circulated in advance, I may not have them. But if so, they should be posted to the website and/or circulated to all participants!

-Paul

From: Subramaniam, Ravi
Sent: Tuesday, April 29, 2014 12:27 PM
To: Schlosser, Paul
Subject: RE: "slides" (Endogenous formaldehyde workshop)

Whatever you are most comfortable with, Paul. On a different note, I should clarify that the discussion session is not necessarily about discussing the presentations but intended to be centered on the questions being asked about formaldehyde and the data.

Ravi.

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From: Schlosser, Paul
Sent: Tuesday, April 29, 2014 12:08 PM
To: Subramaniam, Ravi
Cc: Sonawane, Bob; Ross, Mary; Scott, Cheryl; Kraft, Andrew; Glenn, Barbara
Subject: RE: "slides" (Endogenous formaldehyde workshop)

I think it's appropriate for me to make some slides that address data and points from the three presenters. Part of my analysis was to extrapolate Swenberg's 6-hr data, which he will most likely present, to the dG levels predicted for continuous exposure, which makes for a better comparison to the endogenous dG that come from continuous exposure. So I can have a slide or two on that. I can also review Appling's draft slides, and Peterson's when we get them, to have some questions prepared as slides. ICF may have to deal with getting them on a memory stick tomorrow, but that's the sort of thing that I believe Bob and Cheryl are saying is OK.

-Paul

From: Subramaniam, Ravi
Sent: Tuesday, April 29, 2014 10:39 AM
To: Schlosser, Paul
Cc: Sonawane, Bob; Ross, Mary; Scott, Cheryl; Kraft, Andrew; Glenn, Barbara
Subject: RE: "slides" (Endogenous formaldehyde workshop)
Importance: High

Paul:

I ran your "clearance" concern by Bob Sonawane who informed me that if your slides are part of a discussion (as opposed to a formal presentation) then they do not have to be cleared. I also talked to Cheryl after that. Either way, whatever you decide is fine.

Ravi.

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From: Schlosser, Paul
Sent: Tuesday, April 29, 2014 10:13 AM
To: Mel Andersen; Subramaniam, Ravi; Formaldehyde_wkshp
Cc: Harvey Clewell
Subject: RE: "slides" (Endogenous formaldehyde workshop)

Mel, all,

I am not sure why the nucleus would be any more protected from cellular/endogenous formaldehyde than exogenous formaldehyde, since the exogenous must pass through the cytoplasm, etc., to get to the nucleus, if the endogenous and exogenous are otherwise freely mixed.

I am extremely uncomfortable anyway with the idea of presenting ***any*** slides that have not been cleared, and am hereby withdrawing them. Kim (or whoever is receiving this at ICF), please delete the file that I sent late yesterday.

What's in those slides is basically what I sent around for the presenters to consider, as they prepare their talks, last week. The extent to which they choose to address my points or not is now up to them. I will then comment on what is presented tomorrow.

Mel: FYI, I am not a member of EPA's formaldehyde assessment team, though I am internal reviewer of the draft documents. I think you know well that I am strong believer in the use of good, vetted models for use in risk assessment. But the choice of what to put in the draft assessment is not mine.

As Harvey knows, if you want EPA to use the models you've been developing, we'll need a 'package' or packages that we can run to reproduce all published figures and results, and to QA.

-Paul

From: Mel Andersen [mailto:MAndersen@thehamner.org]
Sent: Monday, April 28, 2014 6:49 PM
To: Schlosser, Paul; Subramaniam, Ravi; Formaldehyde_wkshp
Cc: Harvey Clewell
Subject: RE: "slides" (Endogenous formaldehyde workshop)

Paul,

I am still a bit perplexed by what it means to be a discussant at the meeting. You are introducing a good bit of material that will come out of the blue for the audience and be at a level difficult for them to put into perspective.

I have been fretting over these issues using simple model structures since our 2010 paper on genomics that also had limited modeling of endogenous adducts/cross-links (attached). Our first paper was simply intended to note that the behavior of formaldehyde in tissues was more involved than just accounting for labeled DNA-protein cross links starting from zero-background. We also used binding with GSH to restrict free levels of formaldehyde acetal. We have now extended our modeling/analysis to the more recent Swenberg studies and provided a talk on our preliminary results at the 2013 SRA (attached). We are awaiting publication of Jim's data to complete our current pk structures for endogenous formaldehyde.

You provide one conclusion about formaldehyde binding pools limiting availability for DNA-reactivity. To some extent we began the process of looking at this by including GSH binding in our 2010 paper. Accounting for other reversible, saturable binding pools could further restrict free acetal concentrations and still lead to concentrations that eventually cause dose-dependent increases in tissue acetal as the sites fill.

Another possibility, besides the conclusion, that tissue formaldehyde is not available for reacting with DNA, is that the nuclear compartment may also be protected to some degree from cellular formaldehyde acetal reactivity or that endogenous adducts might be preferentially formed from local pools of 'formaldehyde' generated by reactions in the nucleus – e.g., histone and DNA demethylation (see figure in the SRA talk). We don't know which idea/ideas is/are true or what combinations of factors might best account for the observations. All these ideas need more analysis and thought by a variety of individuals.

In any case, I hope these ideas in aggregate can gain more visibility with EPA as you consider risk assessments that include endogenous compounds, rather than relying on your limited calculations or the conversations at the meeting this week. I would be happy to have further discussions on these topics with you and others at EPA. The way the session is organized with the first three speakers does not really tee up the issues that you want to discuss here.

In any case, I do feel better that I am now forewarned about your slides as I try to serve as co-chair. We may be able to introduce these concepts in the discussion following the three introductory talks.

Issues surrounding endogenous compounds have arisen several times in my career. With a variety of colleagues, we have run into questions about considering endogenous and exogenous sources with work on several compounds – carbon monoxide (as one of the metabolites of methylene chloride), acetone, manganese and formaldehyde. With all of these, PK efforts had to include input of materials from diet (Mn) or from endogenous routes of production (for CO, acetone and formaldehyde).

Despite my irritations about the specifics of the upcoming workshop, it is reassuring to see EPA taking steps to consider endogenous levels of these materials and the manner in which considerations of endogenous levels of various compounds might affect thinking about risk assessments in general. You can see comments about this point in the last few paragraphs of the 2010 paper.

Mel

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, April 28, 2014 4:10 PM
To: Subramaniam, Ravi; Formaldehyde_wkshp
Cc: Mel Andersen
Subject: RE: "slides" (Endogenous formaldehyde workshop)

Here are some slides summarizing my analysis (file attached).

I hope to heck… pun intended, that I don't get into trouble for not having these cleared.

-Paul

From: Subramaniam, Ravi
Sent: Thursday, April 24, 2014 9:51 AM
To: Schlosser, Paul
Subject: "slides"

Sorry. . . I used the word slides (and only in the email to you) rather loosely. What you sent suffices for now (and counts as the slides I was referring to). My suggestion, and I leave it entirely to you, is that if you prepare what you sent around in the form of a couple of slides that can be projected, it will enable you initiate a more pointed discussion. Otherwise my feeling is that it will not get through.

Ravi.

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From: Schlosser, Paul
Sent: Thursday, April 24, 2014 9:44 AM
To: Subramaniam, Ravi
Subject: RE: Formaldehyde Workshop: Session 1 Planning Call

I really wasn't planning to prepare slides ahead. This goes into why I only agreed to be a discussant and not a presenter in the first place.

-Paul

From: Subramaniam, Ravi
Sent: Thursday, April 24, 2014 9:36 AM
To: Schlosser, Paul
Subject: RE: Formaldehyde Workshop: Session 1 Planning Call

Paul

Thank you. This will facilitate a more pointed discussion. I was too pre-occupied with the bimonthly meeting yesterday, so I am glad you sent it out. I mentioned to ICF that your slides would be forthcoming.

Ravi.

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From: Schlosser, Paul
Sent: Thursday, April 24, 2014 9:15 AM
To: Wignall, Jessica; Subramaniam, Ravi; Mel Andersen <MAndersen@thehamner.org> (MAndersen@thehamner.org); Edna Mangum; Appling, Dean; Lisa Peterson; Ross, Jeff; Martyn Smith; James Swenberg
Cc: kim.osborn@icfi.com; Malloy, Maureen; Sharp, Codi
Subject: RE: Formaldehyde Workshop: Session 1 Planning Call

Colleagues,

Ravi recalled that I'd done an analysis based on some of Dr. Swenberg's data in combination with the formaldehyde inhalation dosimetry model of Conolly et al. (2000) to contrast the levels of N^2-hydroxymethyl-deoxyguanine (dG) adducts with what's known or can be estimated for endogenous vs. exogenous levels, and asked that I send it around. I've attached the piece. It's just over 2 pages, though a bit dense.

Part of this may be trumped by recent data that Jim mentioned on the phone.

In short the Conolly et al. model used observed DNA-protein-crosslink (DPX) data and a rate constant for DPX formation from in vitro experiments to effectively estimate the nasal tissue levels of HCHO at various exposure levels. I then extended the model to predict dG formation and clearance (assuming formation is proportional to HCHO levels and clearance is first-order), calibrating the extended model to Jim's dG data from 6-h exposures. I then used the model to predict what dG levels would be given continuous HCHO exposure or a long-tern 5 d/wk, 6 h/d pattern.

Also, I can use the model to back calculate what level of "free" HCHO must be in the cells to be consistent with the observed endogenous dG levels. As stated, reported/measured endogenous formaldehyde levels are ~ 400 uM, but if that formaldehyde was as available to form dG as the exogenous formaldehyde in Jim's experiments, then the endogenous dG levels should be ~ 40 times higher than observed. Put another way, the endogenous dG levels, based on this modeling, are only consistent with a "free" endogenous HCHO level of 10.4 uM, not 400 uM. This much lower level of "free" endogenous formaldehyde is also much more consistent with the relative potency of exogenous vs. endogenous formaldehyde in forming tumors in the rat nose. So this analysis suggests that over 97% of the measurable formaldehyde is reversibly bound or sequestered in a way that keeps it from reacting with DNA … and causing tumors.

While the mathematical models used here are anchored in data, they are clearly extrapolations. As you are putting together your talks, any information your could provide to support, refine, or negate these predictions would be helpful!

Thanks,
-Paul

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